CHRONIC MICROELECTRODE RECORDING ARRAYS

Quarterly Report

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by

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CHRONIC MICROELECTRODE RECORDING ARRAYS

Executive Summary

This contract seeks to develop wireless microsystems for chronic multi-channel recording in the motor cortex of primates, setting the stage for subsequent trials in quadriplegic humans. The approach we are taking uses active or passive multi-channel two-dimensional silicon probes containing 16-64 sites each, arranged in three-dimensional arrays. The probe output signals are routed to circuitry on the rim of the implant assembly using multi-lead silicon- or polymer-based microcables. The rim-mounted circuitry identifies neural spikes and passes the spike occurrences to the outside world over a bidirectional wireless link that derives power and control signals for the implant from an externally-supplied RF carrier. The implanted circuitry can also be used to output a full analog representation of the neural activity on any single site.

During the first quarter of this contract, 16-site multi-shank passive probes have been used in-vivo, and new 16-and 32-site passive probes have been designed for future use. The probes have built-in silicon ribbon cables. A dedicated test facility for 64-site active recording probes has been established, including a LabView interface, and the 64-site active probe is being iterated for use in a non-multiplexed system. These probes have a 64:8 front-end site selector to allow the electronic selection of sites close to neurons of interest. The new probes will incorporate site placements specifically targeted at monkey motor cortex. We have also designed an 8-channel analog spike detector chip for use with the outputs of the probes. Each spike detector averages its input signal, generates a threshold voltage above the noise level, and continuously compares the input signal with it. Whenever a spike occurs above threshold, the circuit outputs the corresponding site address. Each detector draws 50µA from ±1.5V (150µW) and occupies a chip area of 180µm x 163µm (0.03mm^2). The full 8-channel detector chip measures 1.9mm x 2mm, operates from ±1.5V, and dissipates 1.41mW.

Working in Dr. Andrew Schwartz's laboratory at the University of Pittsburgh, six-probe (96-site) implants have been performed in the motor cortex of two monkeys. In the first implant, the agar used to seal the cortical surface was excessively thick, so that four of the six probes failed to enter the brain and recorded no activity; the other two probes recorded low-levels of activity on 8 and 12 of their 16 sites, respectively. A number of design improvements to the MINI implant assembly were identified on the basis of this experiment and were incorporated in the assembly used in the second monkey. In this implant, two (perhaps four) probes were damaged during polypyrrole site-coating procedures. The other two probes produced discriminable units on 20 of their 32 sites. We are developing tools to aid in the probe insertion process.

During the coming quarter, the analog spike detector chip will be fabricated along with both passive and active probes and chip versions of the active probe circuitry. The circuitry for an improved wireless interface chip will be designed and submitted. Primate implants will continue to further refine the surgical techniques and implant assemblies.

Activity Summary

During the first quarter of the base contract, we have worked to define the most viable approach to realizing wireless implants of 64 recording sites in primate motor cortex. The implants must realistically be working by the fall of 2005. Our activities during this past quarter were as follows:

- Five individuals from this program attended the November NIH Workshop on Neural Interfaces at the Bethesda Hyatt and presented the latest results on multi-channel neural recording along with an overview of the present contract.

- The general architecture of the intended recording system was reviewed and defined, and a timeline for the various activities was constructed. There are parallel efforts on passive probes, active probes, interconnect cables, probe interface electronics, an integrated spike detector, a bidirectional wireless interface, and the overall implant assembly as well as on continuing implants in rats and monkeys to guide the overall effort.

- Passive 16-channel probes were designed specifically for recording from monkey motor cortex and will be fabricated during the coming term.

- A dedicated facility for bench-testing the 64-site 8-channel active probes was established and software for rapidly testing the devices was written. Plans for revising the active probe design consistent with the year-one system architecture were defined.

- An 8-channel monolithic spike detector was designed and submitted to the MOSIS foundry service for fabrication. Design efforts are now turning to the bidirectional wireless interface chip, which will build on an earlier design.

- A chronic system housing has been designed for use with six 16-site passive probes. This design was prototyped, implanted, and iterated on the basis of in-vivo results.

- In rats, initial experiments have focused on evaluating the ease of probe insertion into cortex and methods for closing the site; in monkeys, two devices were implanted as an aid in developing appropriate surgical techniques and to evaluate the current system housing design.

Research Results and Discussion

The LABVIEW software interface for a 64-site active recording probe was developed. This software allows the user to send clock, mode, reset, and a 5 bit address to the probe for selecting 8 of the 64 sites for amplification and for time division multiplexing of the signals onto a common data line. Data collection and storage software, which includes demultiplexing, was developed previously. For the year-one system, we will not multiplex the signals but instead will run the eight amplified channels directly to a rim-mounted chip containing probe interface circuitry and thence to a spike detector and wireless interface chip. Modifications to the active probe circuitry for use with analog spike detector chip in the year-one microsystem are in progress. Fabrication of the modified active probes will begin during the coming quarter along with continued in-vivo testing of the present version of these probes.

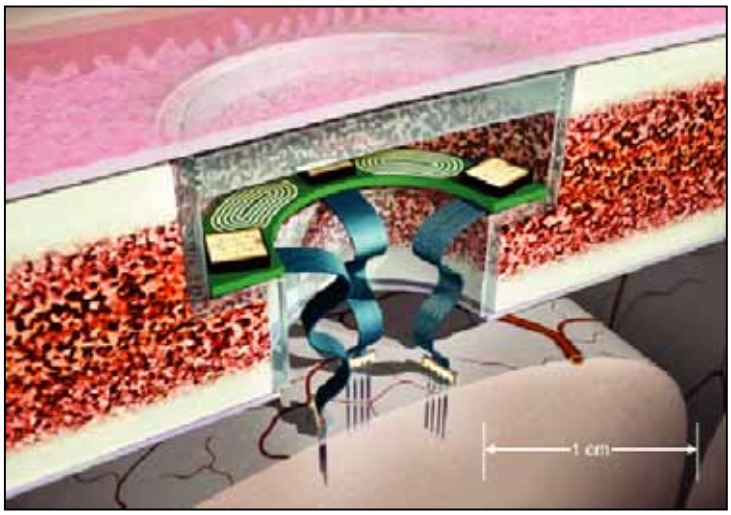

Fig. 1: The MINI microassembly for a cortical implant, here shown with passive 2D probes.

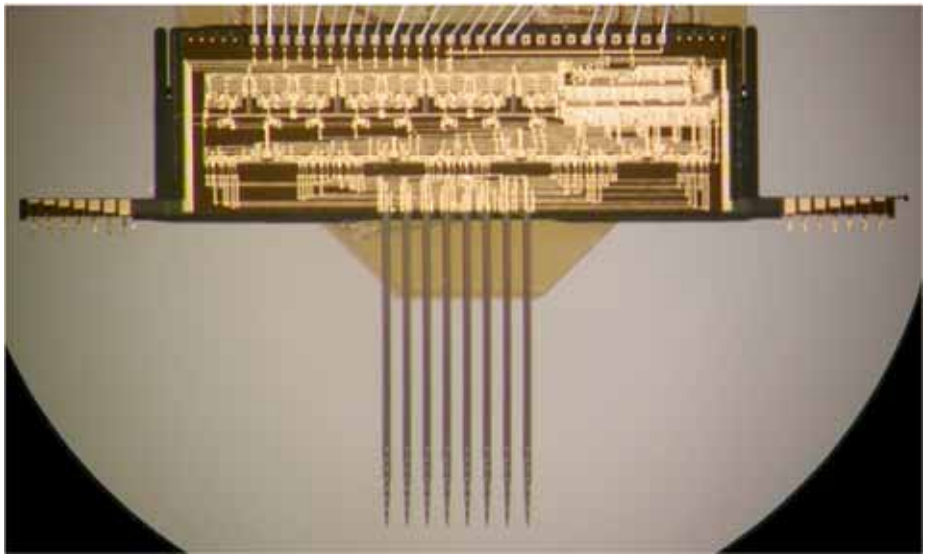

Fig. 2: View of a 64-site 8-channel active probe configured for 3D platform mounting but mounted here for acute use. The revised probe will be non-multiplexed.

The probe (either an active probe containing on-chip site selection and amplification circuitry or a passive probe with rim-mounted amplification circuits) will operate into a spike detector. Although the longer-term (year-four) goal of this project remains a multiplexed active probe with a digital spike detector, the year-one goal is a non-multiplexed probe (active and/or passive) operating into an analog spike detector. During the past quarter, this spike detector has been designed. It generates an adaptive

threshold voltage above the noise level and continuously compares the input signal with it. Whenever a spike occurs above that threshold, the circuit generates a binary-high output. It is robust in the face of variations in the input-signal baseline. The circuit operates satisfactorily in worst-case over the full range of process variations and draws only 50µA from ±1.5V power supplies (150µW). It occupies a chip area of only 180µm x 163µm (0.03mm^2). It should be noted that more than half of this area is consumed by trimming circuitry, which should be eliminated in the next version of the circuit. Simulated operation and a layout of the spike detector is shown in Figs. 3 and 4, respectively. Some analog test circuitry for use in characterization is also included on the chip.

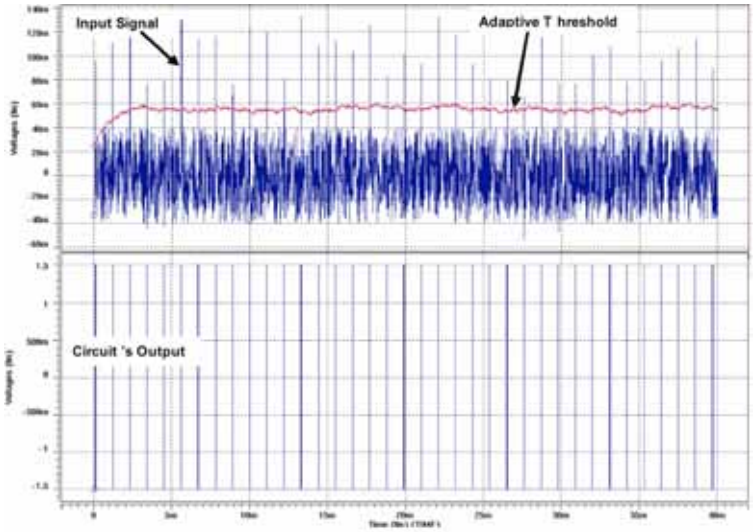

Fig. 3: Simulated output of the analog spike detector (lower trace) to input from a neural recording site (upper trace).

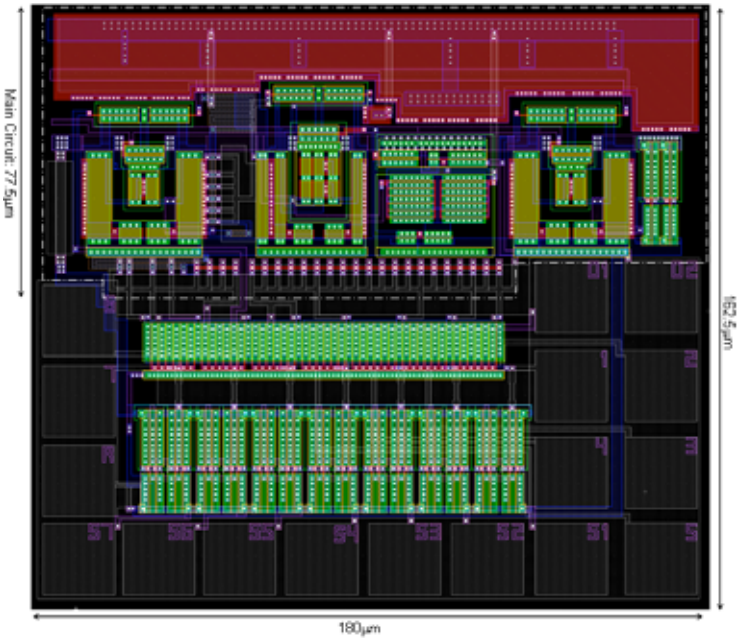

Fig. 4: The layout of the overall analog spike detector test die.

An eight-channel test module capable of operating in the Scan and Monitor modes has also been designed. During the Scan mode, all channels are searched (in parallel) for the occurrence of spikes. When a spike is encountered, a flag bit is output that is subsequently tagged with the appropriate channel address. A digital data compressor receives the tagged channel activity, eliminates the inactive channels, and puts only the active channel addresses on its output port. Thus the information delivered by this chip will be the presence of a spike above threshold, its time above threshold, and its place of occurrence, but not its amplitude. The eventual digital spike detector will deliver digitized amplitude information as well as spike width and place of occurrence. In the Monitor mode, any of the input channels can be selected for continuous viewing at high resolution. Figure 5 shows a block diagram of the eventual year-one recording system

(excluding the telemetry module). A detailed block diagram of the 8-channel test version of the spike detector is shown in Fig. 6. A layout of the spike detector chip, which has been submitted to MOSIS for fabrication, is shown in Fig. 7. It measures 1.9mm x 2mm, operates from ±1.5V, and dissipates 1.41mW.

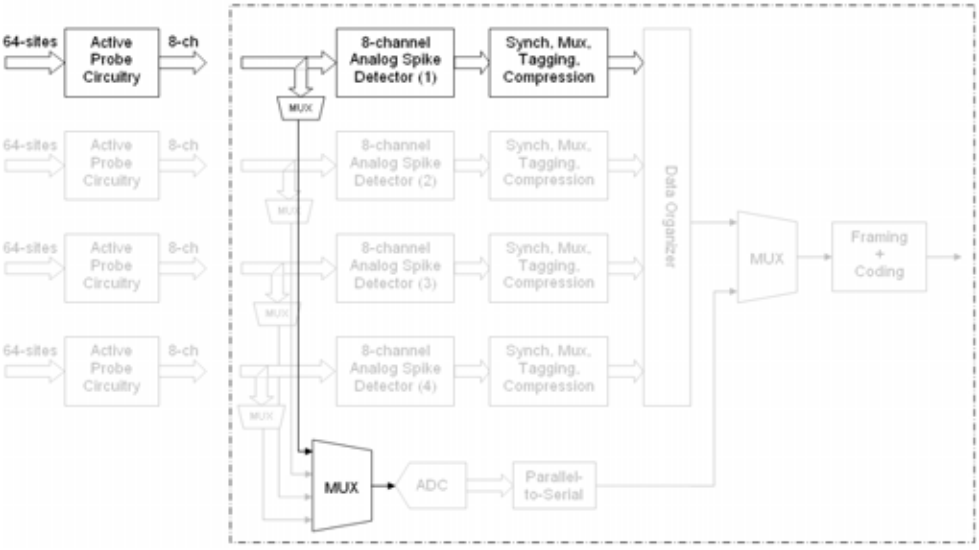

Fig. 5: Block diagram of the 8-channel analog spike detector.

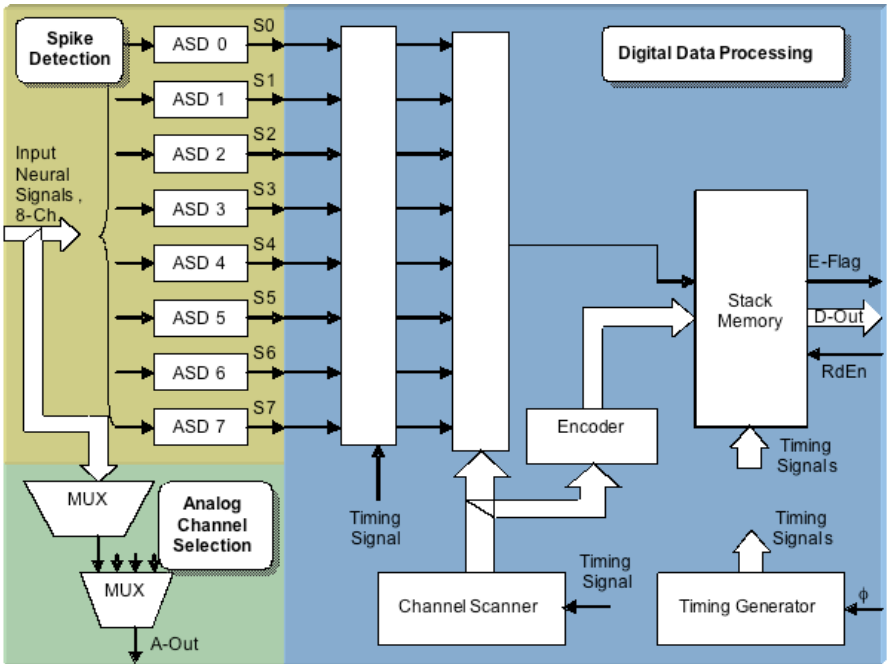

Fig. 6: A detailed block diagram of the analog spike detector test system as submitted for fabrication.

During the coming quarter, we will design the bidirectional telemetry module for the cortical recording microsystem. This system will include a power regulator, clock recovery module, data demodulator, digital control unit, digital output transmitter, input

data converter, and power-on reset circuit. It will build on a functional telemetry interface developed under a previous NINDS contract.

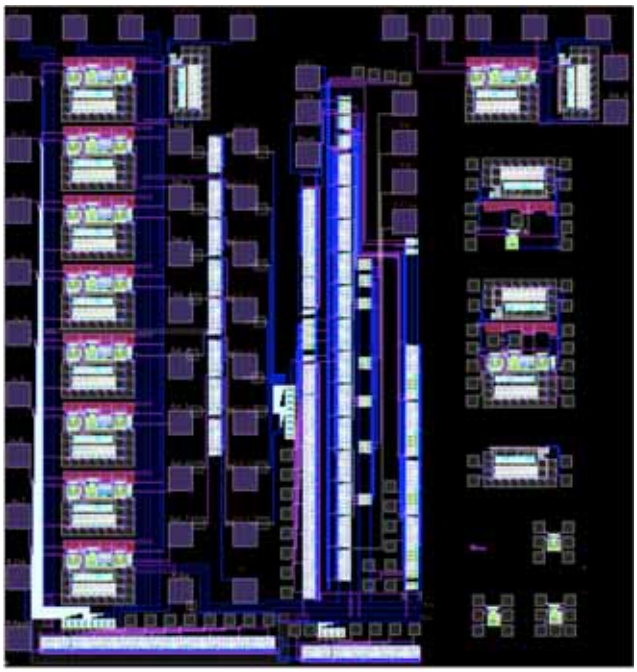

Fig. 7: Layout of the 8-channel spike detector system to be fabricated at MOSIS.

Rat Experiments

The first set of *in-vivo* experiments was conducted in the rat model, primarily focusing on evaluating the ease of probe insertion. These systems were populated with four chronic passive electrode arrays (64 channels). The insertion technique and procedure for closure were also developed in the rat model (described in more detail below). Neural recordings were collected from the implanted rats to ensure the viability of the electrical recording sites post-implant (Fig. 8d).

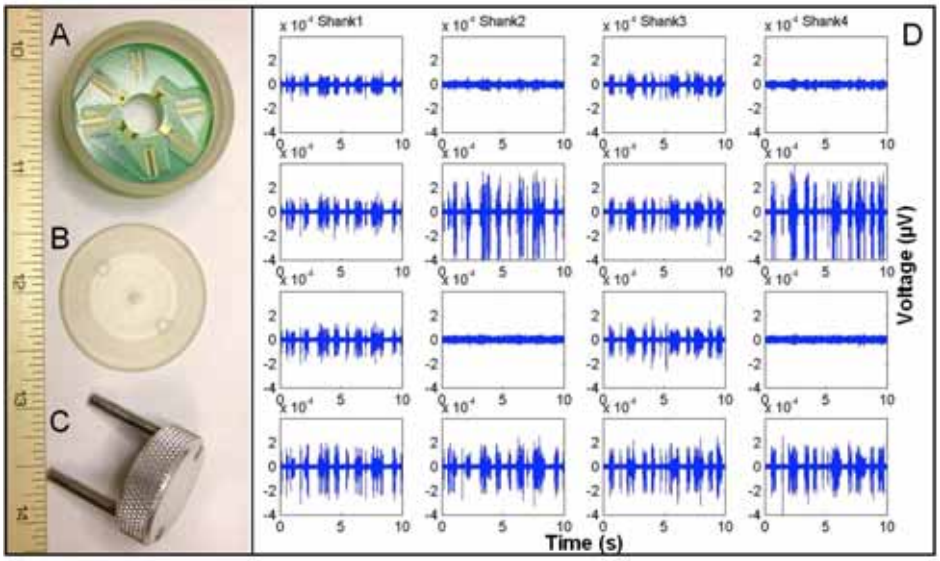

Fig. 8: (a) Polysulphone housing and PCB, (b) housing cap for protection of system, (c) machined tool for removal of cap, (d) neural spike recordings from rat barrel cortex

Monkey Experiments Rationale:

After preliminary bench top and rat model testing/evaluation were performed, monkey experiments were undertaken. Monkey procedures have unique spatial and geometrical requirements, so preliminary monkey experiments were required to further test and evaluate the system. To date, two devices have been surgically implanted in monkeys in Dr. Andrew Schwartz's laboratory at the University of Pittsburgh. The primary focus of

the first procedure was to begin to develop surgical techniques for the implantation of the devices and to begin optimization of the system housing design. The focus of the second procedure was to continue the development of the surgical techniques, to further evaluate the design of the housing, and to explore the modifications that were made on the basis of the previous experiment. The following section summarizes these experiments.

MINI monkey implant (10/7/04)

General details: Overall, the surgery was a general success. Much was learned about the device and desirable modifications for the next procedure. The device was populated with six 16-site 4x4_4mm200chron probes (four shanks each with four 1250μm^2 sites per shank). The entire procedure lasted approximately 4.5 hrs.

Probe Implantation: A 10mm trephine was used to create the craniotomy. The dura was completely removed exposing the brain throughout the entire craniotomy. After removal of the dura, a layer of agar (~3mm) was administered over the cortex (via syringe) filling the entire craniotomy. A thin layer of Kwik-Sil (elastomer polymer, WPI) was applied around the perimeter of the craniotomy prior to placement of the MINI to seal off the brain from the external environment. The MINI was positioned over the craniotomy with its inner lumen resting on top of the agar. It was cemented in place with dental acrylic and the ground wire was attached to two bone screws. The probes were manually implanted one at a time through the agar into the cortex. After the second probe was inserted, slight bleeding occurred. The bleeding was minimal; however it clouded the agar to a point that the surface of the cortex was no longer visible. The subsequent probes were implanted "blindly" due to this non-translucent agar. The thickness of the agar became an issue as it restricted the depth through which the probes could be inserted. On the basis of impedance measurements, it is believed that four of the six probes were suspended in the agar and did not penetrate the surface of the cortex. Once all six probes were inserted, the inner lumen was filled with Kwik-Sil, encapsulating the entire ribbon cable of each probe. Dental acrylic was applied over the Kwik-Sil, providing a protective rigid coating.

Post-operative recording details: Neural recordings were present on two of the six recording probes (16-channels each) 24hr post-implant. The average impedances on the sites showing unit activity were approximately 400kΩ at 1 kHz, while the average impedances of sites on the other four probes (without spike activity) were approximately 1.4MΩ (presumably due to the conductive nature of agar). On one of the two functional devices, 12 of 16 sites had low-amplitude spike activity present. On the second of the two devices, approximately half of the channels had low levels of spike activity. No spike activity was present on any sites of the four probes that exhibited high impedances. Neural recordings were present on the two functional probes through the first week, at which point the connectors were broken. The users have found it difficult to plug in the conventional plastic-base Omnetics connectors, which are easily damaged by users and by the implanted animals. In this animal, the connectors were broken to the point that the headstage amplifiers could not be plugged in. The monkey was sacrificed 1 month later and histological evaluation is currently in progress.

Design Modifications from MINI-1 to MINI-2 (Fig. 9):

- ***Ground wire access port:*** The ground wire exit point was changed from the inner lumen to the upper sidewall of the device.
- ***Inner lumen wall dimensions:*** The depth of the inner lumen wall was decreased from 4mm to 2mm to improve brain access.
- ***Inner lumen shape:*** The inner lumen shape was changed from circular to rectangular to better span the motor cortex. The outer shape of the housing remained circular.
- ***Stability 'feet':*** Stability feet extending out from the outer wall surface were created to help anchor the device when embedded in the dental acrylic.
- ***Pre-bend probe inside inner lumen***: The probes were pre-bent into the inner lumen. This took considerable time during the first surgical procedure.
- ***Apply larger Silastic bead for better leveraging the probes***: The silastic bead, at the junction between the probe and silicon cable, is crucial for insertion.
- ***Replaceability***: The housing design was modified so that a base unit would be permanently fixed to the skull, with a replaceable component temporarily fixed to the base so the probes can be replaced if they become damaged after implant.

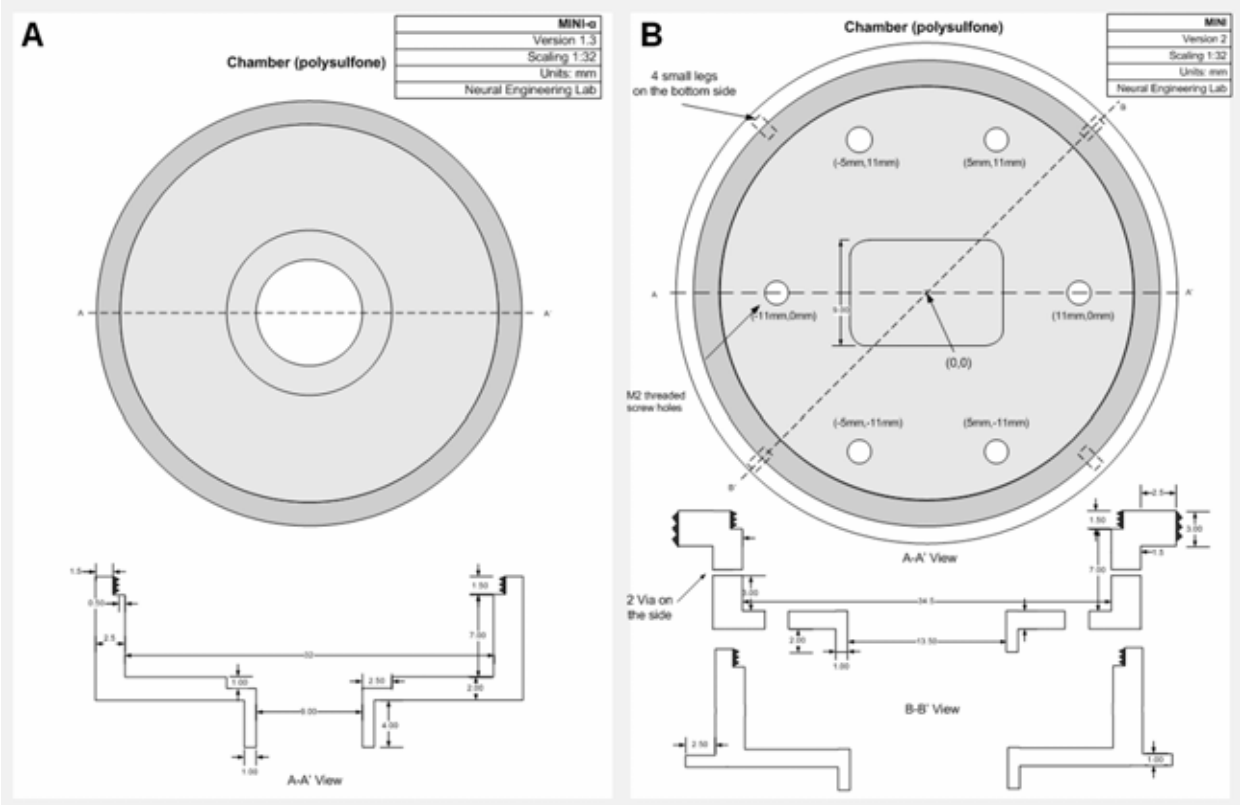

Fig. 9: (a) Preliminary housing design – MINI-1, (b) Modified housing design – MINI-2

MINI monkey implant (12/15/04)

General details: For this surgery, there were several design modifications to the device housing from the previous version. Each modification addressed an issue at hand, and

there were very few required modifications for subsequent iterations. With this implant, we focused primarily on the design and insertion of the probes themselves, rather than the design of the housing, as was done in the first implant.

Bioactive coating details: Professor Tracy Cui at the University of Pittsburgh was interested in coating the probes with a conductive polymer seeded with bioactive molecules. The MINI system was gas sterilized at Michigan and then coated under a sterile hood in Tracy's laboratory. Several complications arose during the coating process, but eventually eight of the sixteen sties on two of the six mounted probes were coated. The probes were UV sterilized for 15 minutes immediately prior to surgery. The probes were agitated fairly extensively during the coating process (through mixing of the coating solution) such that the probes experienced many physical perturbations over several hours. Site impedances were measured prior but not subsequent to coating.

One of the key issues in making stable long-lasting neural recording is to secure the connections between neurons and the sites. Towards this goal, we electrochemically deposited polypyrrole doped with two peptide fragments from ECM protein laminin onto sites 1-8 of probes 3 and 4. The two laminin fragments were P364 and P1543. P364 promotes neuron attachment, and P1543 promotes neurite outgrowth. From neuronal culture data, both peptides, when immobilized on the Polypyrrole surfaces, support neuronal growth, especially on surfaces containing 50:50 mixes of both peptides. This composition was used here. This coating has produced a two-fold decrease in 1kHz impedance magnitudes on iridium sties similar to those used here. Fig. 10a shows that rat cortical neurons attached on the PPy/mixed peptide surface and appear to be healthy, with long processes after 2 days in culture. (Blue stains for DNA and green stains for beta-tubulin (neuron specific marker).) Figure 10b shows the number of viable cells per cm^2 on three different surfaces (the number of cells on gold or Polypyrrole/non-bioactive molecules is zero).

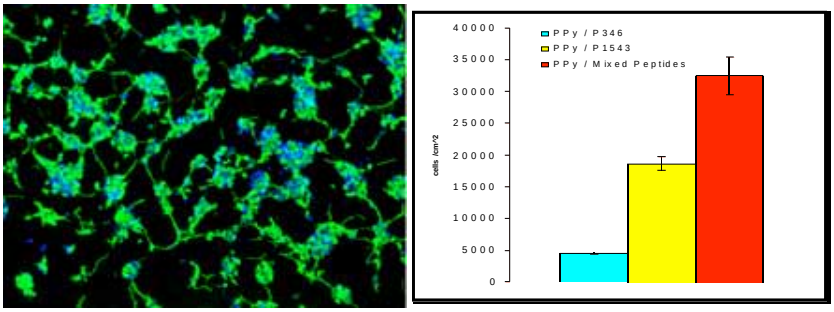

Fig. 10: (a) Rat cortical neurons attached on the PPy/mixed peptides surface, (b) the number of viable cells per cm^2 on three different surfaces

Surgical details: The device was again populated with six 16-channel 4x4_4mm200chron probes. The entire procedure lasted approximately 4 hrs. This was the first device implanted in this animal (Ulysses), who was 3.5 years old. The device was implanted in the right hemisphere. A manually-operated 10mm trephine was used to create the craniotomy. The inner lumen of the MINI was rectangular in shape, rather than circular as in the previous version. With a sterile pen, the shape of the lumen was

drawn on the surface of the skull using a pre-made template. After the circular piece of bone was removed, the remainder of the bone was removed using a pair of Rongeurs. Next, the dura was cut and folded back up along the inner walls of the craniotomy. This was done to deter the dura from regrowing towards the implanted probes. Preliminary studies in rats have found that extensive dural regrowth can build up and push the brain away from the probes, thus pulling the probes out of the brain. Prior to placing the MINI on the skull, a very thin layer (<1mm) of agar was applied to the surface of the brain to help prevent dehydration of the tissue. A thin layer of Kwik-sil was applied around the outside of the inner lumen of the MINI and around the perimeter of the craniotomy on the top surface of the bone. Kwik-sil was used to seal the intracranial space from the outside world. The MINI was positioned so that the inner lumen of the device fit inside the craniotomy. The walls of the inner lumen were designed to prevent bone regrowth towards the implanted probes. The device was grounded to two separate bone screws and was mechanically fixed with dental acrylic (PMMA) to the skull and several bone screws.

Probe Implantation: Using microforceps and beginning with the closest (working lateral to medial), the probes were manually implanted through the agar into the cortex. The probes were pre-bent into the inner lumen prior to the surgery to help ease some of the difficulties of handling the probes. Two of the six probes were damaged during insertion (Fig. 11c). That the remaining four probes were implanted into the brain was visually verified. The total insertion time was about 45 minutes. Dental acrylic was applied over the Kwik-sil to provide a protective rigid coating.

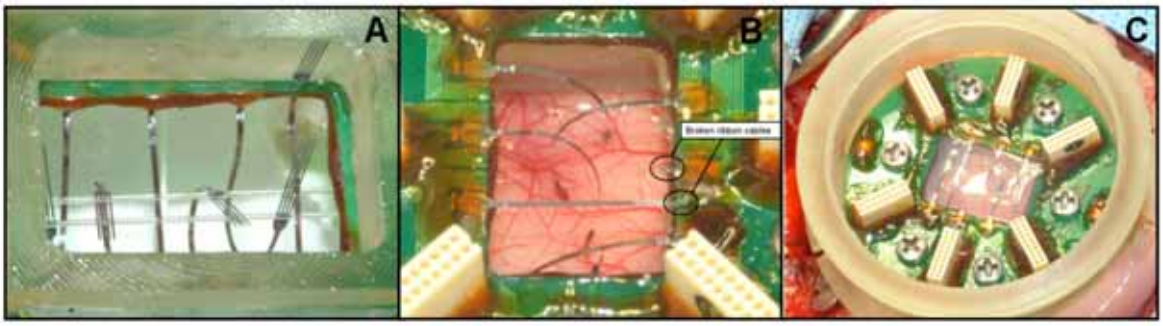

Fig. 11: (a) The underside of MINI showing the method for "docking" the probes until implantation, (b) four intact probes implanted in monkey cortex and 2 broken probes, (c) inner lumen filled with Kwik-Sil.

Post-operative details: The monkey recovered very well and was alert and active within 24 hours post-op. Two of the probes showed impedances ranging from 500–750kΩ. The other two probes showed impedances ranging from 2.2–2.4MΩ. Only two of the four arrays produced neural recordings. On those two probes, there were 20 discriminable spikes across the 32 channels. The other two electrodes appeared to be broken. Recordings were maintained for approximately 1 week after implantation. Preliminary impedance measurements have indicated that there was a fluid leakage problem on the PC board that was shunting the channels together. This was a potential contributor to the decreased SNRs across the functional arrays and is still under investigation. While we have always used standard FR-4 PC boards in our single-probe chronic assemblies, the MINI PCB is particularly prone to leakage; not only is the it much larger and therefore

more difficult to conformally coat, it is also placed inside a closed chamber where it is likely to experience condensation. We therefore plan to move to liquid crystal polymer (LCP) as the board substrate and to encapsulate all exposed connections with silicone. Dr. Edell at InnerSea Technologies has done *in vitro* and *in vivo* testing of silicone-coated LCP structures and has found them to remain viable for at least one year.

Discussion: From the first- to the second-generation implants, there were many design modifications to the MINI housing. The most significant change to the second-generation MINI was the "replaceable" component. The device was designed so that if the probes fail in any way, the PCB (along with the Omnetics connectors) may be removed from the housing, which is permanently mounted to the skull. Individual probes cannot be replaced, but the entire set can be replaced as a whole. The real challenge at this point is the insertion technique. The current procedure is risky because of the way the probes are closely spaced inside the MINI and the way the probes are manually inserted into the brain by grasping them with microforceps. With minor false moves, the entire procedure can go from a complete success to a complete failure. Currently, we are focusing considerable attention on developing an insertion device to eliminate the grasping aspect of the insertion. We are working with machinists to create a "fork" that can be used to push the probes into the cortex. This tool that would be slightly wider that the ribbon cable yet smaller than the portion where the silastic bead rests. Once a probe is parked in place on the cortex, the fork could be used to push the probe downward.

Next Iteration: We plan to perform a replacement procedure on the 2nd implant, replacing the PCB and the implanted probes. In February, we also plan to perform a third surgical implant in a monkey. In this design, the 18-pin Omnetics plastic connectors will be replaced with a more robust high-density 51-pin Omnetics metal-encased connector. This connector will only require the experimenter to make two connections, rather than six as in previous versions.

Concerns

During the first quarter of this new contract, we have generally followed the plan outlined in the original proposal and have met all of the first-quarter milestones described there. We have validated surgical techniques in rodents and have performed implants in two monkeys using the MINI-1 hybrid connector system. The most significant changes to the original plan have been to move to a non-multiplexed active probe design to allow a simpler analog spike detector to be used in lieu of the digital spike detector mentioned in the proposal. The multiplexed digital system remains the goal of the program over its full four years, but the analog system offers a better prospect of achieving the required in-vivo system within the 15-month base period. It will allow us to validate the entire implant system, understanding noise issues and other aspects of the recording environment, even though it will not offer some features we consider necessary for a practical human implant. For example, the present spike detector puts out only the occurrence of a monophasic spike with no information about spike shape, making the separation of multiple units on a given site impossible. The passive probe system will allow a full three-dimensional recording system but will not allow site selection and will be sensitive to leakage on the cables and PCB leads prior to the amplification circuitry.

The active probe system will incorporate site selection and will be highly immune to upstream leakage because of the very low output impedances of the probe output buffers.

Conclusions

During the first quarter of this contract, 16-site multi-shank passive probes have been used in-vivo, and a new set of 16-and 32-site passive probes has been designed for use in future quarters. These probes have incorporated built-in silicon ribbon cables. We have also established a dedicated test facility for 64-site active recording probes, including a LabView software interface, and are in the process of iterating our 64-site probe for use in a non-multiplexed system. These probes have a 64:8 front-end site selector to allow the electronic selection of sites close to neurons of interest. The new probes will incorporate site placements specifically targeted at monkey motor cortex. We have also designed an 8-channel analog spike detector chip for use with the outputs of the probes. Each spike detector averages its input signal, generates a threshold voltage above the noise level, and continuously compares the input signal with it. Whenever a spike occurs above threshold, the circuit outputs the corresponding site address. The detector draws only 50µA from ±1.5V power supplies (150µW) and occupies a chip area of only 180µm x 163µm (0.03mm^2). The full 8-channel detector chip measures 1.9mm x 2mm, operates from ±1.5V, and dissipates 1.41mW.

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During the coming quarter, the analog spike detector chip will be fabricated at the MOSIS foundry and both passive and active probes will be fabricated and tested at the University of Michigan. We will also fabricate chip versions of the active probe circuitry for use with our passive probes. The circuitry for an improved wireless interface chip will be designed and submitted for foundry fabrication. Experiments with implants in monkey motor cortex will continue to refine the surgical techniques and implant assemblies being developed.